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Case Report

Switching to tacrolimus extended-release improved the effectiveness of immunosuppressive therapy in a heart transplant patient: A case report

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SUMMARY

We report on a 25-year-old female heart transplant patient who presented with recurrent episodes of cellular rejection due to decreased adherence to immunosuppressive therapy. She received a heart transplantation in 1994 when she was 10 years old. In order to improve her adherence to immunosuppressive therapy, switching to the once-daily extended-release formulation of tacrolimus was performed in a step-wise fashion. First, the twice-daily formulation of cyclosporin A was replaced with the twice-daily preparation of tacrolimus. When the trough blood levels of tacrolimus reached a plateau in the range of 5.0 ng/mL, it was changed to the once-daily extended-release formulation of tacrolimus after confirming the absence of new rejection episodes. There were no significant changes in renal function before and after the switch. After being discharged from the hospital, the patient made significant advancements in adherence to immunosuppressive therapy. Her subsequent clinical course was uneventful, with no adverse events observed. Most patients who undergo solid organ transplantation must receive lifelong immunosuppressive therapy. This case demonstrates that conversion to the extended-release formulation of tacrolimus from other calcineurin inhibitor preparations is a reasonable choice to consider in the management of compromised immunosuppressive therapy adherence in heart transplant patients during the late posttransplant period.

Introduction

For most patients who undergo solid organ transplantation, strict adherence to immunosuppressive therapy is important for maintaining optimal post-transplant immunosuppression.

Extended-release formulation of tacrolimus (Tac-ER) is a once-daily oral formulation of tacrolimus (Tac). Previous studies in kidney and liver transplant patients have demonstrated favorable rates not only in incidences of biopsy-proven rejections but safety profiles [1]. The modified formulation and the conventional twice-daily Tac show similar exposures as estimated by areas under the curve (AUC) and trough levels [minimum concentration (C_{min})], with a reduced peak maximum concentration (C_{max}). However, data are limited in heart transplant patients. Doesch et al. recently reported a significant improvement in adherence in heart transplant patients after a switch from twice-daily calcineurin inhibitor to once-daily Tac-ER [2].

We report the case of a Japanese heart transplant patient who presented with recurrent episodes of cellular rejection due to decreased adherence to immunosuppressive therapy. Replacing the twice-daily oral formulation of the calcineurin inhibitor Tac with once-daily Tac-ER achieved stable therapeutic blood levels and helped prevent the recurrent episodes of rejection.

Case report

A 25-year-old woman with a history of dilated cardiomyopathy status post-heart transplantation in 1994 presented with exertional dyspnea and bilateral pedal edema in 2009. She experienced episodes of moderate cellular rejection for which she received steroid pulse therapy in November, 1994, five months after the transplantation. During the following nine years, that is, from age 11 to 19 years, her clinical course was uneventful without any episodes of significant rejection by the administration of cyclosporine A (CyA), azathioprine, and low-dose prednisolone. Her coronary angiography which had been annually performed

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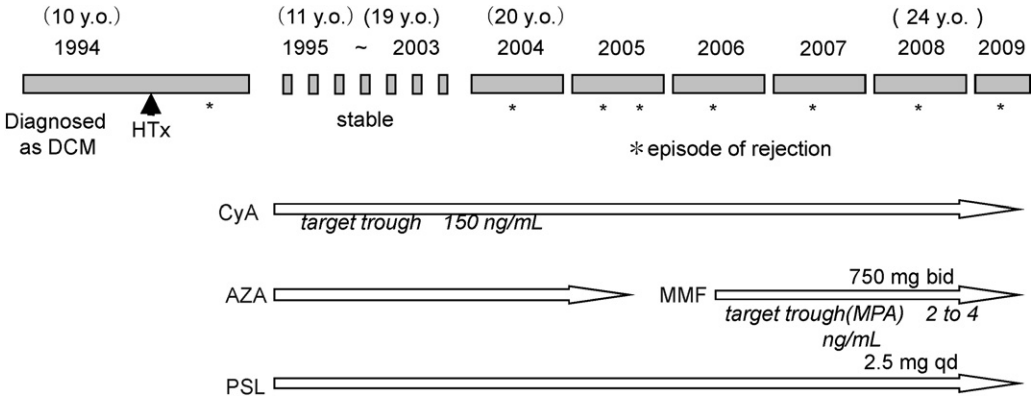

Figure 1. Timeline of the patient's clinical course before the admission. DCM, dilated cardiomyopathy; HTx, heart transplantation; CyA, cyclosporine A; AZA, azathioprine; MMF, mycophenolate mofetil; MPA, mycophenolic acid; PSL, prednisolone.

had showed neither significant stenosis nor occlusion. However, in the four-year period beginning in 2004, she was hospitalized six times due to acute rejection which needed treatment with intravenous methylprednisolone. Measurements taken during those hospitalizations showed that the trough levels of CyA were in the range of 40–60 ng/mL, considerably lower than the target trough level of 150 ng/mL at that time. The major socio-psychological events the patient experienced in the period from 1995 to 2004 (age 11–20 years) included a change in her family structure with her parents' divorce. Since becoming a legal adult in 2004, she was employed in a series of part-time jobs at night to support living by herself and experienced associated changes in her peer relationships. Moreover, she went through an emotionally unstable period in 2005. These events contributed to her non-adherence to immunosuppressive therapy.

The patient began to manifest pedal edema in early March 2009, with increases of her cardiothoracic ratio (64.5%) in her chest X-ray film. Her echocardiogram showed the appearance of interventricular septal paradoxical motion, increased to moderate from mild tricuspid valve regurgitation, increased diameter of inferior vena cava from 8.5 mm to 12.1 mm, and the appearance of mild pericardial effusion. Her laboratory data showed elevated cardiac troponin I (0.15 ng/mL) and serum N-terminal pro-B-type natriuretic peptide (NT-proBNP), 4481 pg/mL. She was admitted to our hospital on March 17, 2009 for treatment of congestive heart failure. Although endomyocardial biopsy at this admission was not performed, the low concentration of CyA measured before admission (50 ng/mL) suggested that rejection resulting from insufficient immunosuppression was at least partially responsible for the onset of her current cardiac disease (Fig. 1). Her physical findings at admission showed mildly tachycardic (104 beats/min), regular rhythm and her blood pressure was 98/50 mmHg. She had a third heart sound and exhibited bilateral pedal edema. Laboratory findings revealed mild hepatic congestion (aspartate aminotransferase 57 IU/L; alanine aminotransferase 82 IU/L), mild kidney dysfunction (urea nitrogen 31.1 mg/dL; creatinine 1.01 mg/dL; 24-h creatinine clearance 42.2 mL/min).

After her admission, the blood CyA level was managed so as to reach the target level of 150 ng/mL.

Her previous history of repeated hospital admissions due to rejection episodes resulting from non-compliance to immunosuppressive therapy strongly suggested that the patient's current

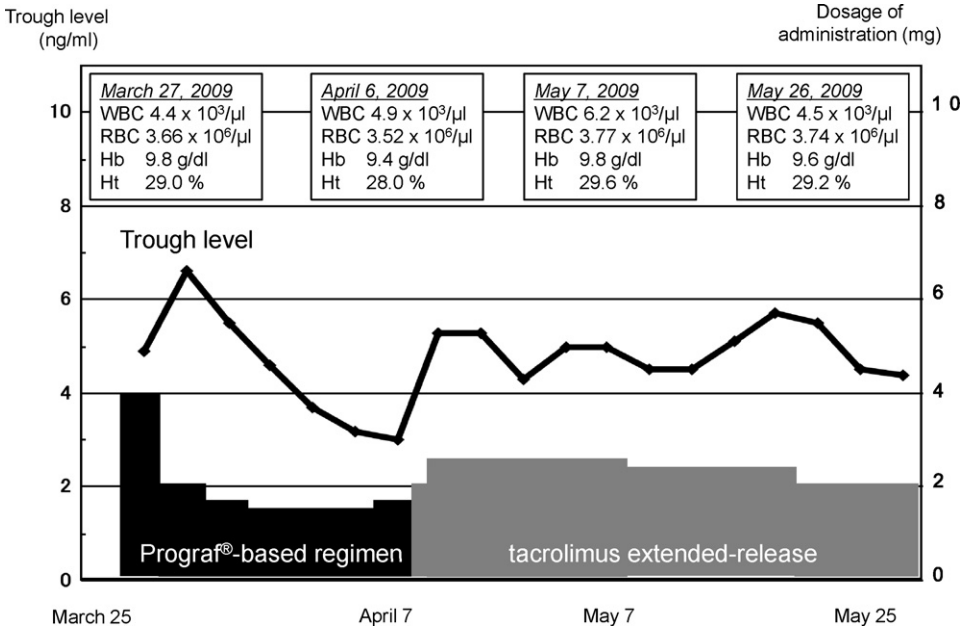

Figure 2. Changes in tacrolimus dosage and trough level in Prograf® -based regimen to tacrolimus extended-release formulation. Complete blood counts are indicated. WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; Ht, hematocrit.

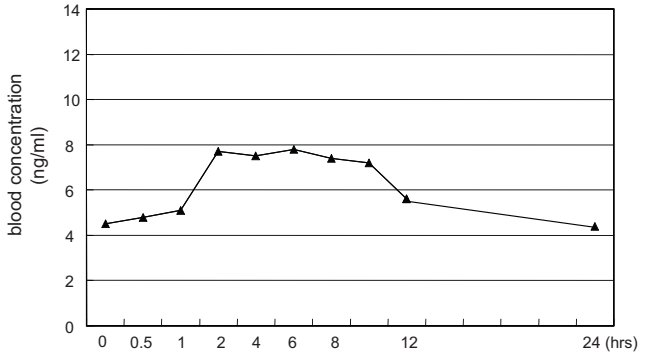

Figure 3. Plot of tacrolimus blood concentration under the administration of 2.0 mg daily tacrolimus extended-release formulation of this case.

hospitalization also involved forgetfulness and carelessness in taking medications as prescribed. She had received not only CyA but mycophenolate mofetil (MMF) and the trough level of her mycophenolic acid had always been between 2 and 4 ng/mL which was her target blood level (Fig. 1). The main reason for many episodes of her rejection was thought to be due to non-adherence of taking calcineurin inhibitor. In order to improve the patient's adherence to immunosuppressive therapy, we decided to switch to the once-daily extended-release formulation of Tac in a step-wise fashion. First, the twice-daily formulation of CyA was replaced with the twice-daily preparation of Tac (Prograf®, Astellas Pharma, Tokyo, Japan). When the Tac (Prograf®) blood levels reached a plateau in the range of 4.0–5.0 ng/mL, it was changed to the once-daily extended-release formulation of Tac (Tac-ER) after confirming the absence of new rejection episodes. Four weeks after this switch, dosages were modified to maintain Tac trough levels at the minimum target concentration of 4 ng/mL (Fig. 2). The patient's complete blood counts during the conversion had not shown significant changes (Fig. 2), and the same dosage of MMF (750 mg bid) and prednisolone (2.5 mg qd) had been maintained. Her echocardiography, electrocardiogram, and laboratory findings were weekly examined during this period, and no occurrence of rejection was detected.

When trough levels became stable, pharmacokinetic measurements were performed. When compared to previously reported AUC plots for Tac-ER [3], the patient's AUC plot was similar (Fig. 3).

After the start of the in-hospital treatment, the patient's bilateral pedal edema improved. Her clinical course was uneventful after the change to the Tac-ER formulation. After the treatment, her cardiothoracic ratio on chest X-ray film decreased to 57.6%, paradoxical motion of interventricular septum and pericardial effusion on her echocardiogram disappeared, cardiac troponin I decreased to 0.03 ng/mL, and NT-proBNP decreased to 742 pg/mL. There were no significant changes in renal function before and after the switch to the Tac-ER; 24-h creatinine clearance was in the range of 42–51 mL/min, and cystatin C levels were in the range of 1.21–1.34 mg/L throughout the conversion to the once-daily formulation. After being discharged from the hospital, the patient made significant advancements in adherence to immunosuppressive therapy; the frequency of forgetting to take medication decreased and the compliance to the timing of taking medication improved. In outpatient clinic follow-up, the patient did not require changes in the dosing regimen. Her subsequent clinical course was uneventful, with no adverse events observed.

Discussion

Tac-ER is a once-daily formulation developed to reduce the frequency of administration for patients currently using a twice-a-day Tac. For a given dose of Tac, the 24-h AUC values for the twice-daily standard-release formulation and the once-daily extended-release formulation are similar [4]. In kidney transplant recipients, AUC_{0-24} was highly correlated to trough level of standard-release formulation and the once-daily extended-release formulation [1,4]. The standard-release formulation has a bimodal concentration–time profile with a higher maximum concentration (C_{max}) than that of the extended-release formulation, whereas the extended-release formulation has a more gradually tapering profile [1,4].

In a study by Weng et al., when once-daily was compared to twice-daily dosing, a once-daily dosing regimen was found to be significantly associated with higher adherence rates (odds ratio: 2.35, $p = 0.003$) [5].

According to Denhaerynck et al., patient-related risk factors for non-adherence include (i) low self-efficacy with medication taking, (ii) age 20 years and younger, (iii) a long period since the transplantation, (iv) pre-transplant history of missed clinic visits, (v) mental or psychological problems, (vi) social isolation and lack of a social support network, and (vii) substance abuse [6].

During the four-year period in which the patient had recurrent acute rejection episodes, her blood CyA concentrations were as low as 40–60 ng/mL. The subtherapeutic CyA levels may be associated with the change in her family structure by divorce and her leaving home to live an adult life alone in March 2004. To support herself, she was employed in a number of part-time jobs at night, which initiated a shift in her peer relationships. Consequently, she passed a psychologically perturbed period in 2005. The patient's history indicates she exhibited risk factors (i), (iii), (v), and (vi) listed above. We concluded that these risk factors were involved in her inadvertently forgetting to take immunosuppressive medications on time or at all and immunosuppressive therapy non-adherence caused the recurrence of acute rejection episodes.

Heart transplant patients who are compliant with immunosuppressive therapy have a significantly longer clinical-event-free period (i.e. time to occurrence of late acute rejection, cardiac allograft vasculopathy, retransplantation, and death), when compared to immunosuppressive therapy non-compliant patients ($p = 0.043$) [7]. For renal transplant recipients, Gaston et al. reported that 35% of late renal allograft losses were associated with immunosuppressive therapy non-adherence [8]. Vlaminck et al. reported that non-compliance in renal transplant patients more than one year post-transplant is associated with an increased risk for late acute rejection during the following five years and they concluded that non-compliance is the most important risk factor in the occurrence of late acute rejection [9].

Under these circumstances, we prescribed Tac-ER for this patient in order to promote immunosuppressive therapy adherence and thereby maintain a therapeutic blood concentration. To the best knowledge of the authors, there have been few previously reported cases regarding the use of the Tac-ER formulation in heart transplant recipients [2]. In renal transplant recipients, however, a high correlation between 24-h AUC and trough values was observed for both the standard-release formulation and the extended-release formulation [4]. In addition, clinically stable kidney transplant recipients who switched from standard to Tac-ER had stable trough and dosage levels two years post-conversion. The incidence of biopsy-confirmed acute rejection (6.0%) and multiple rejections (1.5%) were similar to those for the twice-daily formulation [1]. Silva et al. also reported that Tac-ER in combination with MMF was noninferior to cyclosporine with MMF [10].

In the case reported here, the post-conversion target trough levels were satisfactorily maintained. We succeeded in maintaining the same outpatient Tac dose by improving the patient's

immunosuppressive therapy compliance and preventing further episodes of rejection. Moreover, no renal impairment or other adverse events were observed before and after the conversion.

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